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ACUTE RADIATION INJURY: A REVIEW OF THE PATHOGENESIS, CLINICAL COURSE AND TREATMENT FOR SUBMARINE MEDICAL PERSONNEL

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SUMMARY PAGE

THE PROBLEM

To provide a comprehensive outline for the diagnosis and treatment of acute radiation injury, both penetrating and non-pentrating forms.

FINDINGS

Following a brief introduction on the nature of radioactivity, the pathology, clinical course, and treatment of the Acute Radiation syndrome (including Central Nervous System, Gastrointestinal and Hematologic phases) are examined in depth. The effects of non-penetrating radiations with particular emphasis on decontamination procedures, and the modifications to therapy required by a mass casualty situation are also discussed.

APPLICATION

The material presented in this report should be particularly useful for Hospital Corpsmen and nonradiation-trained Medical Officers when faced with radiation casualty to personnel.

ADMINISTRATIVE INFORMATION

This investigation was conducted and the report prepared by the author in partial satisfaction of the requirements for qualification as a Submarine Medical Officer. Having been accepted as a worthy Qualification Thesis, the manuscript has been approved for publication as a Submarine Medical Center Report, in order to make the information available in the Technical Library and for use in the classes at the School of Submarine Medicine. It has been designated as Special Report No. 67-11, under date of 8 September 1967.

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ABSTRACT

After a brief discussion of the biologic effects of ionizing radiation, the author examines the pathology and clinical features of the Acute Radiation Syndrome, comprised of central nervous system, gastrointestinal, and hematopoietic phases. The currently accepted modes of treatment are included in this discussion. Also included is a section on non-penetrating radiation exposure and decontamination procedures, and some guidelines for management of the many radiation casualties that would been seen in nuclear warfare.

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PURPOSE AND SCOPE

As the use of nuclear power for commercial as well as military uses continues to expand, the likelihood of accidents involving excessive exposure to ionizing radiation will also increase, despite the rigid safety precautions that are employed. An examination of the role of hospitals, physicians, and paramedical personnel in previous radiation casualties has lead this author to believe that a certain lack of understanding exists among the medical professions regarding the nature and treatment of acute radiation injury. This paper, by summarizing the most accepted known information on this subject in a readily accessible and simplified form, endeavors to correct these discrepancies.

INTRODUCTION

In order to appreciate the nature of a radiation casualty one must first grasp some fundamental concepts relating to radiation itself. Radiation is, at its simplest level, a form of energy. This energy is derived or emitted in various forms from the nuclear structure of certain man-made and naturally occurring elements. With the passage of time the ability to emit nuclear energy decreases; this is known as radioactive decay. Each radioactive element has its own constant rate of decay, irrespective of the amount of material or energy present initially. Thus each element also has a particular radioactive half-life, which is the period of time required for some initial energy or activity to decrease by one half of its original value. Another term, biological half-life, is not specific for radiation but simply refers to the time required for the processes of the body to reduce the concentration of any element or substance by one half. The combination of the two expressions is the effective half-life, which describes the time necessary for a given amount of radioactivity within the body to be reduced by one-half, considering both radioactive decay and natural elimination.

Radiation energy may be transmitted in one of four forms: X or gamma radiation, alpha radiation, beta radiation, and neutron radiation. All forms are invisible and can only be detected by sensitive monitoring techniques. X-rays or gamma rays travel as electromagnetic waves and can penetrate all but the thickest of materials while alpha and beta radiations are transmitted in the form of charged particles of energy which will be blocked by very thin shielding.

Neutron radiation travels in the form of a particle also but has no electric charge and is therefore able to penetrate almost as deep as gamma.

The common denominator for the injurious effects of radiation on the living organism is the imparting of a disruptive energy stimulus to the chemical and molecular organization of the living cell. Whether this energy produces toxic products like hydrogen peroxide from cell water, or disrupts chemical bonds between complex proteins like DNA, or whatever, the end result is an alteration in the multiplicity of molecular and chemical relationships. Depending upon the amount of radiation and the sensitivity of the particular cell type, a variety of functional and morphological changes will result. A cell may die, be rendered incapable of reproduction, produce abnormal daughter cells, lose certain of its many functions or suffer no apparent damage. Alterations in tissues are correspondingly varied, ranging from temporary suppression of a few functions to almost complete annihilation of the involved cells. For purposes of quantitating the energy of radiation, several dose units are employed including roentgens, rads and Rem (Roentgen Equivalent Mammal). The latter term shall be used throughout as it best relates to the biological effects of penetrating radiations.

ACUTE RADIATION SYNDROME

The Acute Radiation syndrome, formerly called "radiation sickness", is a term used to describe and encompass the clinical manifestations following the absorption of a uniformly distributed "whole body" dose of penetrating radiation, occurring in a few days. As such Acute Radiation Syndrome applies particularly to X or gamma radiation exposure although it is not exclusive for these sources. From the limited experiences of a handful of reactor accidents, the Japanese experiences of Hiroshima and Nagasaki, and several inadvertent small population contaminations by radioactive fallout, it is apparent that dose distribution to all parts of the body is seldom uniform and that some relative shielding of body parts will almost certainly occur. None-the-less the high penetrability of gamma radiation and the resultant widespread clinical features of such exposure enables one to use the acute radiation syndrome with diagnostic, therapeutic and prognostic usefulness. It must be remembered, however that wide variations in severity, dependent upon dose, dose rate, and distribution, and individual susceptibility, are the rule rather than the exception.

Historically and for clinical simplicity, the Acute Radiation Syndrome has been further subdivided into three categories, each describing the most clinically prominent tissue affected; namely the Central Nervous System syndrome

(CNS), the Gastrointestinal syndrome (GI) and the Hematopoietic syndrome (HS). Although considered separately herein, these syndromes represent the variations in radiosensitivity among certain cells and tissues and thus are manifested to some degree in all patients. Their clinical prominence becomes, therefore, a function primarily of absorbed dose, with time of onset and relative prognosis aiding in their separation.

For purposes of orientation the dose dependency of these syndromes in man, assuming relatively uniform distribution, is as follows. All figures are relative as most of the information on which they are based has been extrapolated from animal experiments or the few accidents involving man in which accurate dose assessment has been possible:

DOSE (Rem)	EFFECT
0-200	Hematologic abnormalities of minor degree, no treatment usually required.
200-300	Hematologic syndrome with Bone Marrow depression; some GI symptoms.
300-500	Moderately severe GI syndrome; the L.D. 50 for man is probably in this range.
500-900	Steadily increasing mortality from GI and Hematologic abnormalities.
Above 900	Up to 100% mortality; in lower dose range from GI syndrome, above 1,600 REM early death from CNS involvement.

NOTE: In general as dose increases the latent period between injury and onset of symptoms decreases and the severity and irreversibility of damage progresses.

CENTRAL NERVOUS SYSTEM SYNDROME

The first and most grave of these clinical entities is the CNS syndrome, produced by doses in excess of 1,600 Rem. Although nerve cells are among the most radioresistant in the body, typical acute degenerative changes will be produced at this dose level and their incapacity for regeneration, the vital role of the CNS in sustaining life and the concomitant severe gastrointestinal injury at this dose level essentially precludes survival. The only exception occurs with a nonuniform dose when a relatively high proportion has been

delivered to the head. In this instance central nervous system symptoms may be transient and survival possible, provided the dose to hematopoietic tissue and the intestines is sufficiently low. Usually, however, nausea and vomiting will begin immediately after exposure, followed promptly by neurological, behavioral or psychological manifestations. Initially there may be listlessness, drowsiness and apathy, proceeding to prostration and coma and more generalized features such as tremors or convulsions. Headache, weakness, hyperactivity, vertigo, ataxia, nystagmus, abnormal sensations of taste or smell, tinnitus, insomnia, fear and confusion are among the possible protean manifestations. Death usually ensues within twenty-four to forty-eight hours. A brief interval of relatively normal behavior and function may occur during this period and should not be interpreted as cause for false optimism. No successful treatment is known. Support of blood pressure and respiration including tracheostomy may be necessary. Right heart failure has been noted and, if present, should be treated in the usual manner. Symptomatic and supportive care including anticonvulsants should be used when indicated. In the few cases studies where death has been attributed to CNS syndrome the pathologic features at necropsy have been fairly unremarkable. Widespread vasculitis, encephalitis and concomitant but not striking cerebral edema have been noted.

GASTROINTESTINAL SYNDROME

The second component of the radiation injury triad is the GI syndrome. As with any radiation injury the pathology, onset, symptoms and prognosis are primarily dependent upon the dose received.

One of the most universal symptoms of appreciable radiation injury in man is the development of nausea and perhaps vomiting appearing soon after exposure. If these symptoms are absent initially or are quite mild and transient, lasting at most a few hours, it may be assumed that severe gastrointestinal injury is not present and that only non-life threatening hematologic changes can be expected and survival without treatment is the rule. At slightly higher dose levels anorexia, apathy and diarrhea may accompany the initial nausea and vomiting, with symptomatology reaching a maximum in six to twelve hours and subsiding within one or two days. This prodromal period correlates with the rapid initial necrosis of the most radiosensitive tissues and may result from circulation "toxins" with histamine-like characteristics. Pathologically the bowel shows depression of mitosis and variable degenerative changes in the epithelial cells, with a few petechial hemorrhages and minimal edema. Within several days the cellular debris is gone, and the partly destroyed epithelial

layer has been regenerated. After the initial symptoms have subsided the patient will enter a stage of asymptomatic well-being lasting from two to three weeks. At this time the effects of bone marrow depression will become dominant. Depending on the dose that has been received, survival is possible and will be discussed under the Hematologic syndrome. No therapy or only symptomatic therapy is required for the initial gastrointestinal symptoms. At this dose level GI ulceration and hemorrhage may occur ten to twenty days following exposure; however this is a consequence of hematologic abnormalities rather than primary intestinal damage.

At high dose levels, in excess of 500 Rem, gastrointestinal tract injury is notably more severe and the prognosis is grave. The appearance of nausea, vomiting and diarrhea will be prompt and often intractable. Occasionally these symptoms will subside after two or three days only to reappear on the fifth day. Malaise and anorexia aid in restricting normal food and fluid intake. Stools may progress from loose and watery to bloody. High fever, exhaustion, and delirium follow and if untreated will be fatal, usually within a week. Pathological examination of the bowel reveals complete cessation of mitosis in the crypts of Lieberkuhn and loss of cell production soon after injury. Cells in the crypts undergo pkynosis and karyorrhexis and bizarre multi-nucleated cells replace them. Normal epithelial cells migrate out to the tips of the villi and are extruded. As new cell production has ceased the cells remaining to cover the ville become fewer and fewer. By the third day increasingly large areas of bowel are denuded, and an outpouring of fluid and electrolytes into the bowel lumen occurs. Ulcerations are usually superficial extending only to the muscularis mucosa, and perforation is rare.

Interestingly the intestinal epithelium may partially or completely recover even from doses which are otherwise lethal for the man or animal. Recovery begins about the sixth day, and regeneration of normal crypts and epithelium is complete in approximately two weeks post-irradiation. The small intestine is the most sensitive portion of the gut and is the first affected. Similar changes occur in the esophagus, stomach and colon but are delayed a few days. From the above discussion it is evident that heroic measures to maintain an adequate fluid and electrolyte balance during the first six to ten days after injury will increase the number of individuals surviving to the second week. Frequent serum electrolyte determinations, accurate and continuous monitoring of intake and output, and massive replacement of plasma and appropriate electrolyte solutions are indicated, particularly when dealing with only a single radiation casualty.

Unfortunately, the dose levels which produce the severest form of the gastrointestinal syndrome are usually sufficient to produce a total and often irreversible ablation of bone marrow and other hematopoietic tissues, the effects of which begin to be seen clincially by about the second week. Thus the vast majority, if not all such severely injured patients, will eventually succumb with the best of therapeutic efforts only postponing the outcome by a few days or weeks.

HEMATOPOIETIC SYNDROME

The third and clinically most important facet of radiation injury is the hematologic syndrome. It is in this area that knowledgeable diagnosis and skillful therapeutic management of the patient bears the fruit of decreasing morbidity and mortality.

The formed elements of the blood and their progenitors in lymph nodes, spleen, and bone marrow are the most radiosensitive cells in the human body. That this is not a uniform sensitivity is well documented in the literature, both from animal and in vitro studies of humans. Figure 1 shows schematically this relationship. From this one can see that both the mesenchymal parent and most of the mature circulating blood cells are relatively radioresistant, the adult lymphocyte being the single exception. It should also be noted that maximum sensitivity occurs in the actively proliferating precursors in bone marrow, lymph nodes and spleen and diminishes as the cells differentiate and mature. Support for these observations is provided by examining the rate of change of the various elements in peripheral blood following irradiation. Production of new cells is impaired or stopped, but the circulating elements escape injury and live out their normal life span. Thus the decrease of peripheral elements is dependent on the length of their usual life span or other means of utilization. The relatively long-lived red blood cell will therefore decrease much more slowly than granulocytes or platelets. The lymphocytes which are quite sensitive throughout their entire developmental cycle will incur direct and immediate damage and disappear precipitously. Even among the sensitive precursors certain differences exist with both myeloblasts and megakaryocytes being much less sensitive than lymphoblasts or erythroblasts. The end result of this hierarchy of sensitivity is that the clincial features of the hematologic syndrome are delayed usually for several weeks after injury, yet can be anticipated and predicted by blood studies within a few days after the initial damage. As with other clinical features of radiation injury, the time of onset and degree of severity of hematologic symptoms is dose dependent.

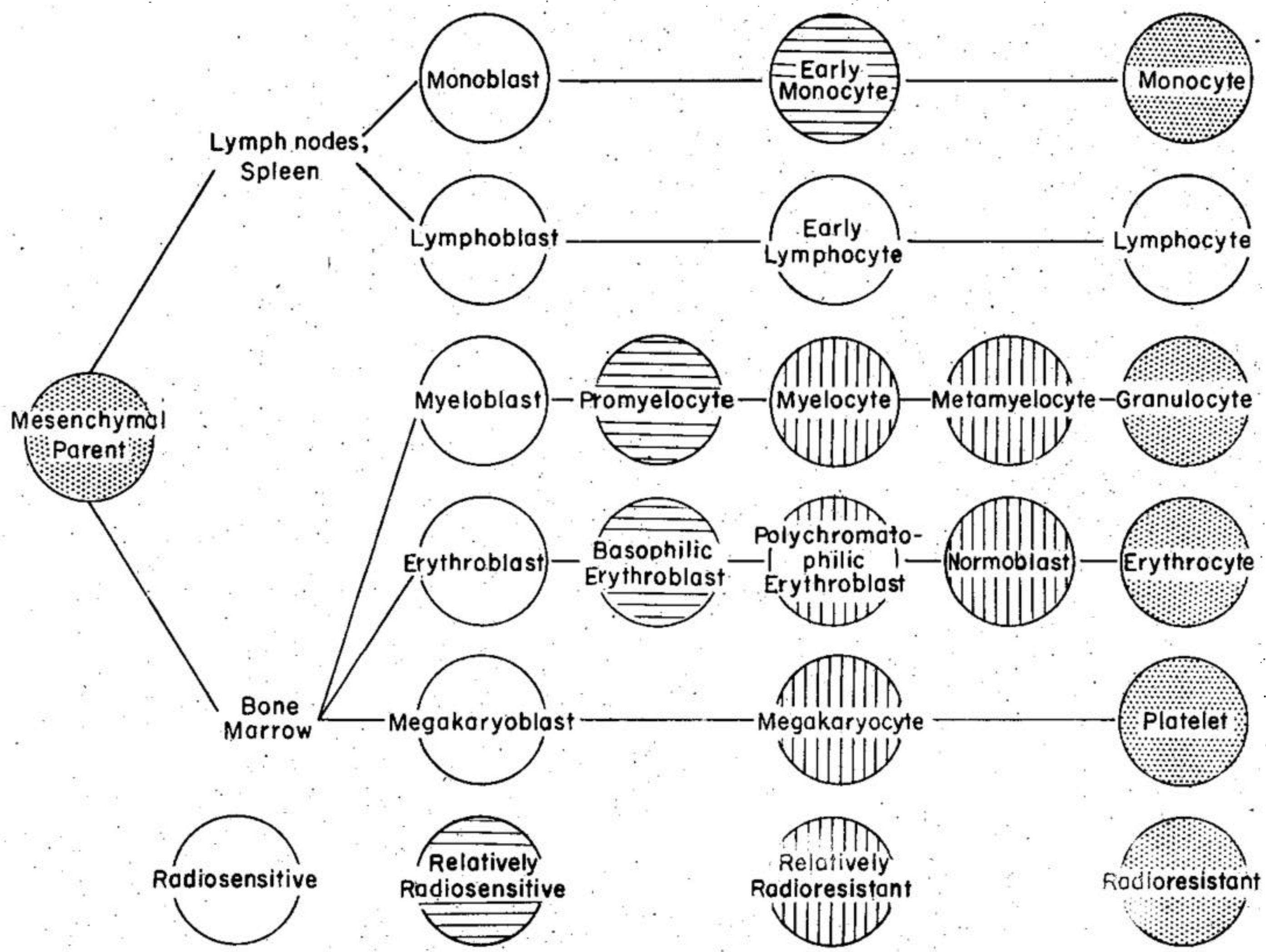

Figure 1 - Relative Radiosensitivity of Blood Cells (modified after Cronkite, E.P.; The Hematology of Ionizing Radiation)

Lymphocytes

The exquisitely sensitive lymphocyte provides the first indication of radiation damage to the hematopoietic system. Lymphocyte levels in the blood begin to decrease immediately after exposure, even at dose levels of twenty-five to fifty Rem. The magnitude and rate of change are closely related to dose up to about two hundred Rem at which point depression is maximal with few if any cells present in the peripheral circulation after twenty-four hours. At the lowest dose levels the maximal depression of the second or third day is followed by regeneration beginning on the fourth or fifth day. With doses greater than two hundred Rem however, the lymphocyte depression is prolonged greatly, with normal values not being reached for months or even years after injury. Parallel alterations take place in lymph follicles and other collections of lymphoid tissue throughout the body. As a prognostic or diagnostic index the dissolution of lymphocytes is therefore quite limited. If less than maximal depression is noted after twenty-four hours, a dose of less than two hundred Rem can be assumed; however clincial symptomatology will probably be a simpler indicator. At higher doses, peak depression provides no help in evaluating the severity of the exposure.

Granulocytes

The alterations in the granulocytic series are more informative to the physician if less dramatic. Although much of our knowledge is derived from animal experiments and their complete applicability to man is uncertain, several common characteristics are evident. During the first twenty-four to forty-eight hours after exposure, an abortive granulocytosis can be seen over dose ranges. The exact mechanism of this is unknown; however speculation includes release of granulocytes from bone marrow and capillaries and a transient mobilization to combat associated injuries. In any case the rise is short-lived and neutropenia gradually begins to be seen, usually after a few days. In the highest dose ranges, probably above 700 Rem, the fall of white cells is precipitous, reaching lowest levels within a week or two. Recovery does not occur, as death rapidly ensues. At doses approximating the L.D.50 for man, the fall is more gradual and minimal levels are not reached for three or four weeks. As the percent mortality and dose decreases a further prolongation of the rate of fall is observed. Indeed near normal granulocytic values may be maintained for several weeks with peak depression not occurring until thirty to fifty days after injury in the sublethal dose range. The slow recovery phase shows similar behavior with the lowest exposures having the shortest periods of depression and most rapid recovery. As with lymphocytes, however, full recovery will take many months. The total white blood cell

count (WBC) behaves in a similar fashion and clearly parallels the granulocytes. Thus the serial determination of WBC or granulocyte count provides a revealing index of probable dose received, chance for survival and the onset of recovery. As actual dose measurements will seldom be available, at least early in the course of illness, this biologic dosimeter may be quite important in estimating the extent of injury and the timing of therapy.

Erythrocytes

Changes in the red blood cells are much less striking than in the white cells. Initially there is little change with near normal levels lasting for several weeks. Then, as the end of the red cell life span approaches, a gradual dropping of the hematocrit is noted with minimal levels occurring six to eight weeks after injury for sublethal and lethal doses. Even with very high doses of radiation, the final dramatic fall is delayed until the second or third week usually. The decrease in red cells is mediated by three factors: (1) Decreased production in bone marrow; (2) Increased peripheral destruction and (3) Hemorrhage. In the absence of hemorrhage, moderate to severe anemia is a relatively late sequelae and is not a difficult therapeutic problem. However, the thrombocytopenia occurring between the second and fourth weeks may result in a variety of complicating hemorrhagic phenomena, and at high exposure levels a disastrous fall in hematocrit in the last twenty-four hours often heralds death. On the other hand, the catastrophic fluid loss seen with the gastrointestinal syndrome may produce a markedly increased hematocrit preterminally.

The rapid (within forty-eight hours) disappearance of reticulocytes from the bone marrow is a sensitive indicator of doses in the lethal range. After several weeks their return and progressive rise is a good prognostic sign but does not always denote recovery.

Examination of the bone marrow is also valuable for sublethal exposures of between fifty and two hundred Rem. In this range a dose-dependent decrease in the mitotic index (the number of mitotic figures per thousand cells enumerated) occurs, with the index approaching zero on the fourth day after exposure for irradiation in excess of two hundred Rem. Serial bone marrow determinations, particularly during the first week, may thus be helpful in anticipating serious hematopoietic sequelae.

Platelets

The last of the blood elements to be considered are the thrombocytes or

platelets. During the first four days after exposure, platelet counts remain normal or are elevated. Then begins a gradual decline in numbers which proceeds at different rates for each species. In man, peak depression does not usually occur until about thirty days, although this may be shortened to two or three weeks at very high dose levels. After a variable period of depression, most often several weeks, the regenerative process begins, and platelet counts slowly climb towards normal, if death does not intervene. Like the granulocytes, the platelet response, though more delayed is closely related to dose and associated mortality. Platelet levels approaching zero in the first few weeks is an ominous sign; the technical difficulties of platelet counting at very low levels, however, would seem to make total WBC or granulocyte counts a more reliable source of prognostic information.

In addition to the quantitative changes in the blood, a number of morphological alterations are produced. Fragmented or bizarre nuclei, vacuolization, toxic granulations, circulating immature cells of all types and other degenerative changes may be observed and will complicate the evaluation of blood smears.

SEQUELAE OF HEMATOPOIETIC DEPRESSION

The clincial features characterizing the hematopoietic syndrome are the result of the pancytopenia produced by bone marrow and lymphopoietic tissue damage. They are similar in almost all respects to the aplasia secondary to certain drugs, etc. except that spontaneous recovery of hematopoietic capabilities following radiation injury is the usual rule, if the patient can be kept alive during the critical third through sixth week. The essential features are hemorrhage, anemia and increased susceptibility to infection.

Hemorrhage

The bleeding tendency that is seen is primarily the direct result of a severe thrombocytopenia. Although there are individual variations in susceptibility, bleeding is usually not a problem with platelet levels in excess of 50,000/mm^3. Possible manifestations include subcutaneous hemorrhage, oral ulcerations and bleeding gingivae, menorrhagia, gastrointestinal ulceration and hemorrhage as well as generalized hemorrhagic diathesis. In the sublethal and L.D.50 dose range, these problems will usually present about the third or fourth week.

Anemia

As discussed previously, the cessation of red blood cell production will lead to the gradual development of a variable degree of anemia, usually in the fourth or fifth week. Signs and symptoms may typically include malaise, headache, fatigue, pallor, tachycardia or dyspnea on exertion. Although the anemia is usually insidious, the hemorrhagic effects of thrombocytopenia may cause a sudden fall in hemoglobin and hematocrit requiring rapid correction.

Infection

The increased susceptibility to infection following irradiation is the result of several factors and has been extensively studied. One such alteration is the impairment of antibody production, particularly the synthesis of previously acquired antibodies when the antigen is re-introduced. The integrity of the body's outermost defenses is also compromised by skin and mucosal ulcerations, allowing numerous portals of entry for bacteria. Lastly the profound granulocytopenia drastically alters the host's ability to combat infection, both by the absolute decrease in white cells and an impaired ability in the remaining cells to effectively phagocytize and kill bacteria. Although a variety of organisms have been implicated, normal enteric pathogens are especially prominent. Signs and symptoms include fever, mucosal and cutaneous infections, cellulitis, pneumonia and septicemia. The occurrence of infection is closely correlated with the progressive neutropenia.

TREATMENT

Unlike the therapeutic inadequacies of managing victims of high level radiation exposure, the skillful treatment of the hematologic syndrome can lead to a marked reduction in mortality. Of cardinal importance is the necessity for careful thought and planning before any therapeutic endeavor is attempted. Usually at least two weeks are available after the initial symptoms of nausea, vomiting, anorexia and fatigue subside.

1. Careful initial history and physical examination is mandatory with particular emphasis on any chronic diseases or conditions which might modify the expected course of the illness.

2. Appropriate medical and health physics authorities should be notified. They, or someone connected with the casualty, may be able to provide some estimate of the dose received.

3. Where exposure is confined to X or gamma penetrating radiation, decontamination procedures or shielding of medical personnel is unnecessary. If doubt exists, monitoring and decontamination procedures outlined elsewhere in this paper should be followed.

4. Where neutron exposure is possible an immediate blood sample should be drawn as the measurement of sodium activation may provide dosimetric information.

5. Rings, watches, dental fillings etc. should be monitored as they may have been made radioactive by the exposure.

6. All patients should be hospitalized as rapidly as possible until the amount of exposure can be evaluated by appropriate clincial and laboratory studies. If the dose has been less than two hundred Rem, the individual can usually be handled on an out-patient basis with careful and frequent follow-up visits.

7. When potentially lethal doses have been received, it is well to institute reverse isolation procedures immediately, as well as providing for specialized nursing care.

8. Appropriate cultures should be taken on the patient; nose and throat cultures on any personnel who might have subsequent contact with the patient might well prove useful.

9. Any medications being taken by the patient prior to exposure should be re-evaluated.

10. The gastrointestinal upset of the first few days can usually be symptomatically managed with antiemetics, etc. Intravenous fluids will seldom be necessary. Tranquilizers or sedation may be helpful as the patient is likely to be quite apprehensive about his illness.

11. Good nursing care is mandatory, particularly regarding oral and skin hygiene. Strict adherence to aseptic technique is required of all procedures involving cutaneous puncture.

12. Initial laboratory studies should be obtained without delay, particularly hematologic studies. A review of their significance is provided on the following page.

(a) Lymphocytes - fall within 24-48 hours even after low doses; if marked depression is not noted, a dose below 200 Rem is indicated.

(b) Hemoglobin/Hematocrit/RBC Count - usually near normal during first 1-2 weeks if fluid balance normal. Gradual decline follows and is guide for frequency of whole blood transfusions. Should monitor closely after third week when hemorrhage from thrombocytopenia is likely.

(c) Bone Marrow - early examination may provide useful baseline. Mitotic Index of zero on fourth day suggests exposure in excess of 200 Rem. Absence of reticulocytes in first 2-4 days suggestive of doses in lethal range; their return is good prognostic sign but recovery not always certain.

(d) Platelet Count - often elevated initially; peak depression usually during fifth week; more rapid and severe depression heralds poor prognosis; along with hemorrhagic manifestations is guide for platelet transfusions.

(e) Granulocyte/Total WBC Count - best overall guide to progress and prognosis; may rise initially; subsequent degree and rapidity of fall closely related to dose and mortality; maximum depression (to very low levels) for $L.D._{50}$ dose range probably by third or fourth week.

(f) Recovery of all hematologic parameters a good sign but return to pre-exposure levels may take months or years.

13. The therapy of anemia or hemorrhage is whole blood transfusion as needed. Clinical condition may be as important as Hgb/Hct determinations in selecting levels for transfusion.

14. Hemorrhage due to thrombocytopenia can be well controlled by the administration of fresh platelets, preferably as fresh concentrated platelet packs. The physician should be alert for the first sign of hemorrhage including hematuria, retinal hemorrhages and petechiae. Special precautions should be taken to avoid minor trauma to the patient e.g. soft diet, good dental hygiene, lubrication of nostrils, avoiding any strenuous activity and avoiding intramuscular or subcutaneous injections where possible. At the height of platelet depression transfusions may be required every few days.

As concentrated platelets are difficult to prepare and must be given within six hours after separation, it is important to anticipate the need for them in advance.

15. Fluid and electrolyte balance should be carefully monitored and abnormalities corrected promptly. Daily weights and an accurate record of intake and output are essential.

16. Vital signs should be taken at frequent intervals. Tachycardia may be noted with initial symptoms when anemia is present or with fever. Respirations are usually normal. The blood pressure is often slightly depressed at first even at sublethal doses; with higher doses it may drop precipitously. This has been noted both in the hypovolemic states of the gastrointestinal syndrome and when no obvious underlying cause exists. Vasopressors have been used with some success, but the use of central venous pressure readings and isoproteranol has apparently not been studied.

17. The weight of evidence is against the use of corticosteroids as the adrenal gland does not appear to be unusually damaged by irradiation. In a few cases their use has shown no clear-cut advantages, and the potential antibody suppression, ulcer induction and electrolyte disturbances associated with steroids has obviated against their use.

18. Adequate nutrition and vitamin supplements should not be neglected.

19. As in most areas of medicine, the prophylactic use of antibiotics should be avoided. The development of resistant strains and the overgrowth of normal flora are obvious reasons.

20. The development of infection in the weakened pancytopenic patient, however, is of critical concern. Fever even when without obvious cause, evident superficial infections, unexplained pneumonitis, etc. should be rapidly and vigorously treated with full therapeutic doses of appropriate antibiotics. The usual gamut of cultures should be taken, particularly blood cultures, but therapy should be initiated immediately and more specific antibiotics added when sensitivity studies become available. The choise of initial antibiotics is probably not critical. Tetracycline or Oxytetracycline, Penicillin and Streptomycin, and sulfonamides have all been used. Oral antifungal agents have been suggested when broad-spectrum drugs are being employed. More importantly, agents should be used in maximal doses and one should not hesitate to change combinations when increasing fever or other clinical signs indicate the development of resistant organisms.

21. A final therapeutic suggestion concerns the use of homologous bone marrow transplants. Research in this area has shown that the need for massive amounts of marrow and frequent host rejection of the tissue limit the value of this procedure unless the radiation dose has been very high.

22. In summary then, the ideal treatment of the hematologic phase of radiation injury consists of (1) careful planning, (2) the use of no drug or therapy without definite clinical indications, and (3) continuous and meticulous observation of the patient's progress throughout the illness. Frequent personal observation by the physician is as important as the laboratory aids. See Figure 2 on the following page.

THE EFFECTS OF NONPENETRATING RADIATIONS AND DECONTAMINATION PROCEDURES

In the previous portion of this paper we have been discussing the effects of acute exposure to the penetrating forms of ionizing radiation, that is X or gamma rays. These rays are not stopped or attenuated by anything but the thickest and most dense shielding materials. On the other hand, once the individual has been far enough removed from the vicinity of the radiation source, his total exposure will not increase nor is he "radioactive" for other personnel. The dose he has received cannot be diluted or reduced but no decontamination is necessary.

There is a second source of radiation, however, which requires a completely different type of management. This group is comprised by the radioactive materials or isotopes which emit radiation energy in the form of charged particles of variable energy called alpha or beta. Like gamma rays these charged particles are capable of causing ionization and therefore damage to biologic systems. Unlike gamma rays, however, most of their energy is dissipated soon after contact with another substance, and their ability to inflict damage is lost. Thus, they are called nonpenetrating radiations because they are easily stopped by minimal shielding. In the case of alpha radiations, a piece of paper, clothing, or even the keratinized outer layer of the skin is sufficient to suppress them. Beta particles, which also vary in their initial energy, generally have a somewhat higher energy level and are thus able to travel deeper into tissues before their harmful effects are lost. They seldom possess enough energy to penetrate below the skin of man, and external damage will usually be confined to this layer. Even heavy clothing will reduce greatly the amount that reaches the skin.

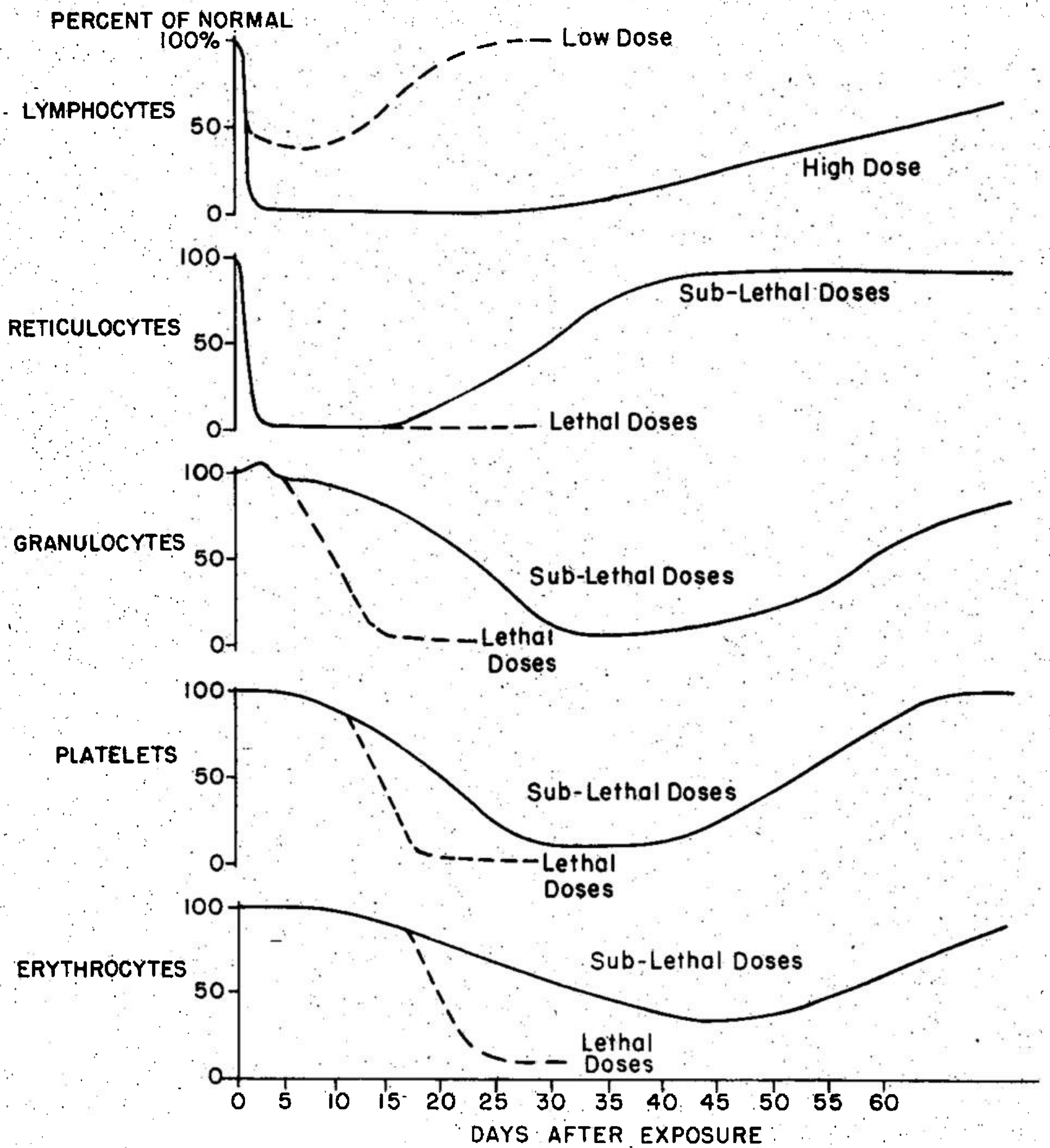

Figure 2 - Hematologic Effects of Ionizing Radiation

A different situation exists, however, when these particles are allowed to enter the body, either by inhalation, ingestion, through breaks in the skin surface such as wounds, or even in a few instances by direct percutaneous absorption. The substances which emit these particles may exist in any physical state - gas, liquid or solid, with finely dispersed solids or dust being a particularly dangerous form of the latter. Although substances which can emit gamma rays can be similarly dispersed, they are a less prominent source and will be neglected in this discussion.

It is readily apparent that when alpha or beta emitters are allowed ingress to the body their capacity for harm is vastly increased. Depending on the substance/s route of entry, solubility, etc., it may be widely dispersed throughout the body, concentrated in a particular tissue or organ, or remain essentially where it entered. There it will continue to emit the damaging particulate radiations until the material has decayed to a low enough level (often a matter of many years) or until the body is somehow able to eliminate it. Its ability to cause damage has been increased by several factors. First the much less dense soft tissues inside the body are less able to stop the energetic particles, and the increased penetration, even if only a few millimeters, will allow many more cells to be exposed. A second factor is time. Once inside, the radioactive substances are very difficult to remove, and the total dose to an area will continue to accumulate as long as the material remains in close proximity. Other factors include the greater radiosensitivity of many internal cell types and the fact that the body may tend to concentrate a particular substance into a given area, such as iodine in the thyroid gland, thus greatly increasing the dose to that area.

THE CLINICAL EFFECTS OF NONPENETRATING RADIATION

It can be readily appreciated from the foregoing discussion that the specific effects of alpha and beta radiation exposure will be highly variable and a complete examination is not within the scope of this paper; however a few general guidelines are discussed.

SKIN - When radioactive substances, particularly beta emitters, are allowed to remain on exposed skin surfaces they will produce a radiation burn consisting of erythema and edema. These burns should be treated by standard methods including pain relief, evaluation of affected parts and prevention of infection. Full thickness burns are not common but scarring and chronic changes may persist. If caused by gamma radiation serious systemic exposure can be assumed.

EPILATION - The loss of body hair, usually twelve to fourteen days after superficial irradiation, may be seen even after relatively low doses. Regrowth is variable. If epilation is an accompaniment of gamma radiation, severe underlying damage has occurred.

INHALATION/INGESTION - Radioactive substances entering via these routes may elicit pneumonitis or damage the gastrointestinal epithelium initially. No specific treatment is available, but steps should be taken to eliminate the material as soon as possible. The latter development of fibrosis or scarring in the affected area is well known.

GENERAL - The greatest problem associated with internally deposited radioisotopes concerns the chronic and cumulative effects common to any radiation exposure. Shortening of life span, increased incidence of developmental anomalies (or often sterility after acute whole body exposure) and a greater threat of malignancy particularly of the skin, blood-forming organs or concentrating tissues such as bone or thyroid are well documented. Most health physics authorities have information relating the maximum permissible internal concentrations allowed before these effects are noted as well as sophisticated bio-assay procedures for estimating the deposited dose. These should be consulted.

CARE OF THE CONTAMINATED CASUALTY

Having become acquainted in the preceding pages with the nature of radiation injury in man, it is now necessary to evolve some practical guidelines for the care of the victim of a radiation accident.

The most important part of treating internally deposited sources of radiation is prevention. The following procedures should be instituted as soon after a casualty as possible and no later than the arrival of the patient at the hospital. If in doubt, it is best to assume that the patient is contaminated by radioactive dust or liquid.

1. Neither the patient nor any other personnel in the immediate area should be allowed to eat, drink or smoke until decontamination is completed.

2. Any type of respiratory screening device will reduce inhalation, ranging from handkerchiefs or surgical masks to more sophisticated breathing apparatus. Similarly, caps, gowns, shoe covers and gloves will provide good protection from alpha and beta radiations for medical personnel. These should be regarded as contaminated following use and should be properly disposed of.

3. Any article or area which the patient contacts should be considered contaminated and should be delineated by tape or similar device. Only properly attired and necessary personnel should be allowed in such areas.

4. All of the patient's clothing should be removed promptly (using gloves) and placed in a sealed plastic or paper bag labeled "contaminated". Assuming no gamma emitting dust is present, these bags will not present a hazard to others unless actual contact is made.

5. The patient should then be showered or bathed as soon as possible. Mild soap and running water are best with particular care being given to avoid even minor abrading of the skin. For this reason scrubbing and brushing are contraindicated. In most cases the patient can wash himself. Pay particular attention to the exposed areas of the body - nails, hands, arms, head, neck, hair and ear canals.

6. At some point in the decontamination the patient and "contaminated" areas must be monitored for residual activity. There are a variety of measuring instruments available, each usually relatively specific for a particular form of radiation. If they are on hand initially, their use may save considerable time and effort; if not, they can be quickly procured from local public health or health physics authorities.

7. When leaving an area of suspected contamination, medical personnel should remove outer clothing (preferable surgical attire), be monitored, and move carefully into a "clean" area.

8. Film badges or other dosimetric devices should be distributed to attending medical personnel as soon as possible to aid in evaluating any radiation exposure they may subsequently receive.

9. The patient may have suffered associated trauma in the accident resulting in contaminated abrasions and lacerations. These should be washed with soap and copious amounts of water and may need to be scrubbed gently. Special probes are available to assess residual contamination. If any activity remains, the wound should be debrided, and block dissection may sometimes be necessary. Amputation has never been required. During the initial body washing, the wounds should be covered with tape to prevent further contamination from entering the wound.

10. A number of chemical cleansers exist that may facilitate decontamination; some of them, however, enhance absorption of certain isotopes and should probably be avoided in most hospitals.

11. Ingested radioactivity should be initially treated as any other poison. Emetics or gastric lavage should be followed by precipitating agents, and antacids such as aluminum hydroxide which may decrease absorption by the formation of insoluble hydroxides. Hastened elimination by the use of cathartics, particularly magnesium sulfate, may be useful.

12. The fate of inhaled radioactive substances will vary with the particle size, with smallest particles passing almost immediately into the blood stream. The nose and nasopharynx should be irrigated with isotonic saline and then sprayed with a vasoconstricter to decrease absorption. Expectorants may enhance the normal removal of contaminated particles from the bronchial tree. Some of this may be re-swallowed and should be treated as an ingestion.

13. Once the basic procedures have been carried out the patient may be moved to other hospital areas without danger to attending personnel. Subsequent bodily excretions such as urine, feces, sputum and vomitus may still be contaminated and should be collected, monitored and properly disposed of.

14. Once a radioactive substance has entered the blood stream, the previously described procedures become ineffective and other steps and agents must be employed. The particular procedure will vary with each substance and its route of entry, solubility and fate within the body. A few general rules are applicable which basically aim to aid and increase the body's natural processes of elimination.

Some radioisotopes are highly soluble in water and are distributed throughout the body within minutes after contact. An example of this group is tritium, a radioisotope of hydrogen, usually found as a gas or vapor. Substances of this type may be removed by hastening the turnover of body water by forcing fluids and using diuretics. The resultant increased renal excretion may reduce the effective half-life to only a few days.

Another group is characterized by an affinity for a particular organ or tissue. Iodine^{131} is such a substance, and its removal can be aided by administering a non-radioactive form of iodine or a similar metabolic competitor e.g. Lugol's solution. As the thyroid cannot discriminate between the radioactive and the stable forms, a dilution of uptake occurs and the excess is eliminated. Also in this group are the "bone-seekers" or elements whose metabolism is similar to calcium such as strontium or radium. These elements remain in the soft tissues for several weeks after entering the body

but are gradually deposited in cortical bone from which their removal is almost impossible. Early use of a low calcium diet, parathormone or ammonium chloride may enhance excretion however.

The last group to be considered are the metals like plutonium, and here complexing or chelating agents may be useful. These agents, by binding the metal, may prevent their interaction with cellular constituents, thus reducing their uptake. Among the agents used are BAL, sodium citrate, EDTA and the relatively new DTPA. Care must be taken in their use, however, as they may actually enhance the gastrointestinal absorption of some metals or prevent normal excretion by their binding. Expert advice should be sought when their use is contemplated, and the reader is referred to standard pharmacological tests for doses, indications, and routes of administration.

MASS CASUALTY SITUATION

In the previous sections we have been discussing the care and treatment of the single uncomplicated radiation injury or at most a few such injuries. It has been assumed that diagnosis and treatment will take place in a hospital setting with no practical limit to medical supplies or nursing and medical personnel. Indeed it is likely that such suppositions will be valid for the rare industrial or peacetime military radiation accident. Unfortunately, since the first atomic bomb exploded over Hiroshima more than twenty years ago, another source of human radiation injury must be considered - nuclear warfare. Although many consider that such a situation would result in world-wide annihilation, it behooves the responsible physician and others in the medical professions to be mentally prepared to function effectively in such an emergency. What then are the differences and similarities between a single injury and the probable thousands of such injuries that nuclear war would produce?

Perhaps the most important single factor worth noting is that the effects of whole body irradiation will be identical in both situations. The same sequence of dose-dependent symptomatology and pathology will be present, and the general principles of treatment will remain the same. There will be, however, a variety of complicating factors in a mass casualty.

1. There will be a large number of non-radiation injuries produced by blast, heat and flying debris. These will include burns, a variety of fractures and lacerations, some of which will be radioactively contaminated

wounds, as well in internal injuries. Other than the treatment of contaminated wounds (covered previously) these injuries should be handled routinely.

2. Although transportation of the injured and removal of the population from the affected area is of prime importance, there will likely be severe disruptions in the normal channels of communication and transportation, particularly within several miles of ground zero.

3. From the Japanese experience it is evident that hospitals and medical personnel, with their tendency towards grouping in large city centers, will be among the most severely affected. Doctors, nurses, corpsmen and technicians who survive will be a precious commodity. Hospital facilities will be swamped and medical supplies, particularly antibiotics and intravenous fluids, will be inadequate.

4. The availability of basic needs including food, water, light and power will be sharply curtailed or lost.

5. Radioactive fallout will involve large geographic and population areas producing both external burns and the problem of inhaled or ingested radioactivity. Their treatment has been previously outlined.

6. Perhaps the most difficult task confronting the surviving physician will be the necessity for realistic triage or casualty sorting. Accustomed by thought and practice to giving each patient the best possible care while even the slightest hope for survival remains, he will be called upon to deny care to some that others might survive. The actual performance of triage may vary considerably depending upon the availability of medical personnel (all types), supplies and facilities, but the basic guidelines will be universal. The material and manpower must be distributed so that the maximum number survive.

To aid in triage, Cronkite has devised a practical clincial classification system, consisting of three categories. (1) Survival improbable, (2) Survival possible and (3) Survival probable. Those individuals in the first category will be those with either CNS effects or severe GI involvement manifested by prompt nausea, vomiting and diarrhea that is intractable. Although the heroic expenditure of I.V. fluids may delay the outcome, the sequelae of bone marrow aplasia and pancytopenia will yield a probable 100% mortality. Individuals in this category should not be treated or cared for. The survival possible group will consist of those persons in whom nausea and vomiting is brief, lasting at most a few days. They will develop the

hematologic syndrome in varying degrees of severity within two or three weeks. They have a statistical chance of survival without treatment which can be markedly improved by judicious use of antibiotics, replacement of glood and fluids, adequate nutrition, etc. It is on this group that maximum expenditure of supplies and personnel should be directed. In the last category - survival probable - will be those without initial symptoms or in whom the symptoms are mild and fleeting. They may present hematologic abnormalities secondary to bone marrow depression at a later date and should be observed but generally will present no therapeutic problem, surviving with no or minimal treatment. Nausea or vomiting due to the emotional trauma attendant upon a nuclear holocaust must be considered when sorting patients.

Several other points should be kept in mind in relation to mass casualty triage. In classifying patients, the entire scope of injury must be evaluated. Chronic disease, the extremes of age, severe traumatic injuries and other factors may necessitate placing someone in the "survival improbable" group even though actual radiation exposure is minor. Further, when evaluating the availability of supplies for distribution it must be remembered that some of the greatest demands will not occur until several weeks after injury and the overall needs of the first critical month must be considered even during initial triage.

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13. ABSTRACT

After a brief discussion of the biologic effects of ionizing radiation, the author examines the pathology and clincial features of the Acute Radiation Syndrome, comprised of central nervous system, gastrointestinal, and hematopoietic phases. The currently accepted modes of treatment are included in this discussion. There is also a section on non-penetrating radiation exposure and decontamination procedures, and some guidelines for management of the many radiation casualties that would be seen in nuclear warfare.

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Acute radiation syndrome - phases, treatment						